Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Frailty-Associated Plasma Proteomics in Relation to Mortality and Multi-Morbidity from A Prospective and Trajectory Study

Jiatang Xu
the First Affiliated Hospital of Sun Yat-sen University, Sun Yat-sen University
Zhensheng Hu
Southern Medical University
Yangfan Su
Sun Yat-sen Memorial Hospital, Sun Yat-sen University
Liling Lin
Sun Yat-Sen University
Runnan Shen
Sun Yat-Sen University
Chaoyu Xie
Sun Yat-sen Memorial Hospital, Sun Yat-sen University
Junhua Hu
Sun Yat-sen Memorial Hospital, Sun Yat-sen University
Kai Huang
huangk37@mail.sysu.edu.cn

Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Article

Keywords: frailty, poly protein score, trajectory analysis, multi-morbidity

Posted Date: September 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10326299/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Plasma proteomics may provide a more dynamic reflection of individuals' frailty status and disease risk. In this UK Biobank study (n = 36,332), we identified 956 plasma proteins significantly associated with frailty index (FI). A frailty-associated poly protein score (PPS) was constructed based on 210 further selected proteins. Trajectory analyses were conducted to characterize PPS evolution over 15 years preceding clinical outcomes. Mendelian randomization (MR) was employed to infer causal relationships between proteins and FI. PPS is closely associated with 6 mortality-related outcomes and demonstrates superior predictive and risk stratification performance compared to the FI. Additionally, PPS was significantly correlated with 32 (96.97%) of the 33 examined diseases from six systems. Trajectory analysis revealed a dual pattern of PPS, showing a significant increase 15 years before death and an accelerated rise in the years immediately preceding death. MR analysis identified 12 plasma proteins with causal associations with FI, and drug prediction identified 98 potential drugs. These findings collectively underscore the importance of plasma proteomics in the management of frailty. The dual-pattern trajectory model of PPS provides both long-term risk stratification and short-term warning signals for mortality and disease. The identified protein targets and candidate drugs offer potential avenues for frailty intervention.

1. Introduction

Frailty, a clinical syndrome reflecting the decline in multi-system physiological reserve, is emerging as a significant health burden[1, 2]. Previous studies have confirmed that frailty increases the risk of mortality and multi-system diseases, including cardiovascular, hepatic, and neurological disorders[3–5].

In exploring its biological mechanisms to inform strategies for preventing and delaying frailty, some researchers have focused on elucidating its underlying causes from a genetic perspective. Several genetic variations associated with the frailty have been successfully identified, providing initial clues for assessing individual frailty risk and exploring long-term intervention strategies at the genetic level[6, 7]. However, the heritability of frailty is estimated to be 30–45%, indicating that frailty is influenced by both genetic and environmental factors[8]. While genetic variations determine individuals' inherent susceptibility, they do not account for the dynamic influence of environmental exposures, lifestyle choices, and the ensuing complex pathophysiological processes that affect an organism's state throughout life.

This recognition of frailty as a phenotype shaped by gene-environment interactions creates a compelling rationale for investigating intermediary biological layers that integrate these influences. Within this conceptual framework, plasma proteomics emerges as a uniquely powerful and novel investigative lens. Circulating proteins serve as functional biomarkers of the interplay between individuals' genome and environmental exposures. Their levels are not only governed by genetic variation but are also acutely responsive to systemic pathological states related to frailty, such as chronic low-grade inflammation, dysregulated metabolic signaling, and impaired tissue repair[9, 10]. Therefore, compared to static genetic

information, plasma proteomics may provide a more direct and dynamic reflection of an individual's current frailty status and their risk of disease and mortality. Furthermore, as more targetable biomarkers, frailty-associated proteins and their regulatory pathways hold promise as potential targets for future pharmacological interventions[11, 12]. Existing proteomic research has concentrated on discrete proteins linked to adverse outcomes in frail individuals, or has targeted frailty outcomes as the prediction objective[13, 14]. Given the dual nature of frailty as both a critical health risk factor and an emerging clinical syndrome, a systematic, large-scale elucidation of frailty's plasma proteomic signature, along with a rigorous exploration of how this signature connects to diverse disease risks, is essential for advancing the field.

We designed a comprehensive study with the following objectives: (1) We identified key proteomic profiles associated with frailty and subsequently constructed a frailty-related poly protein score (PPS). (2) To rigorously validate the association between PPS and 6 mortality outcomes as well as 33 distinct diseases across six systems. (3) To employ trajectory analysis, uncovering the long-term temporal dynamics of the PPS over the 15 years preceding major clinical events. (4) To investigate the causal relevance of PPS-associated proteins using Mendelian randomization (MR) and perform functional annotation to decipher the key biological processes and pathways encapsulated by the PPS, thereby exploring its utility for identifying candidate targets for therapeutic development.

2. Results

Included participants

A total of 36,332 participants were included in this study following the screening process (Fig. 1). Among the participants 2,654 (7.30%) were identified as frail and 13,399 (36.88%) as pre-frail according to frailty index (FI). Frail participants were more likely to be obese, have a lower level of education, a poorer socioeconomic background, and more underlying medical conditions. The baseline characteristics of the participants by frailty status are shown in Table 1.

Table 1
Baseline characteristics of participants

Age, years	**Total**	**Nonfrail**	**Prefrail**	**Frail**	**P value**
	(36332)	**(20279)**	**(13399)**	**(2654)**	
	56.83 ± 8.16	**55.88 ± 8.24**	**57.87 ± 7.97**	**58.80 ± 7.53**	**< 0.001**
Sex, male	16907 (46.53%)	9744 (48.05%)	6039 (45.07%)	1124 (42.35%)	< 0.001
BMI, $kg \cdot m^{-2}$	26.70 [24.20, 29.80]	26.10 [23.70, 28.80]	27.50 [24.70, 30.60]	29.40 [26.20, 33.60]	< 0.001
Waist circumference, cm	90.00 [80.49, 99.00]	88.00 [79.00, 96.00]	92.00 [82.00, 101.00]	97.00 [87.00, 107.00]	< 0.001
Ethnicity, n (%)					
White	34427 (94.76%)	19291 (95.13%)	12659 (94.48%)	2477 (93.33%)	< 0.001
Other	1905 (5.24%)	988 (4.87%)	740 (5.52%)	177 (6.67%)	
Education, n (%)					< 0.001
College or University	12259 (33.74%)	7794 (38.43%)	3990 (29.78%)	475 (17.90%)	
Other	24073 (66.26%)	12485 (61.57%)	9409 (70.22%)	2179 (82.10%)	
Total household income, n (%)					< 0.001
Less than £18,000	7065(19.45%)	2816(13.89%)	3135(23.40%)	1114(41.97%)	
£18,000 to £30,999	12914(35.54%)	6805(33.56%)	5072(37.85%)	1037(39.07%)	
£31,000 to £51,999	8150(22.43%)	5004(24.68%)	2827(21.10%)	319(12.02%)	
£52,000 to £100,000	6433(17.71%)	4335(21.38%)	1943(14.50%)	155(5.84%)	
Greater than £100,000	1770(4.87%)	1319(6.50%)	422(3.15%)	29(1.09%)	

BMI: body mass index; CRP: C-reactive protein; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; Categorical variables are presented as numbers (percentages), while continuous variables are expressed as median (interquartile range, IQR) or mean (standard deviation, SD).

Age, years	Total (36332)	Nonfrail (20279)	Prefrail (13399)	Frail (2654)	P value
	56.83 ± 8.16	**55.88 ± 8.24**	**57.87 ± 7.97**	**58.80 ± 7.53**	**< 0.001**
Unemployed, n (%)	2538 (6.99%)	827 (4.08%)	1063 (7.93%)	648 (24.42%)	< 0.001
Deprivation index	-2.15 [-3.65, 0.53]	-2.40 [-3.80, -0.07]	-1.96 [-3.56, 0.83]	-0.34 [-2.80, 2.82]	< 0.001
CRP, mg/L	1.39 [0.68, 2.82]	1.17 [0.59, 2.34]	1.63 [0.80, 3.24]	2.51 [1.20, 5.12]	< 0.001
HbA1c, mmol/mol	35.30 [33.00, 37.90]	34.80 [32.50, 37.10]	35.79 [33.40, 38.60]	37.20 [34.50, 41.50]	< 0.001
eGFR, mL/min/1.73m^2	106.88 [95.90, 115.13]	107.47 [97.17, 115.57]	106.17 [94.50, 114.64]	105.00 [91.43, 114.02]	< 0.001
Alcohol intake					0.286
Less than once a week	10775 (29.66%)	5114 (25.22%)	4376 (32.66%)	1285 (48.42%)	
More than once a week	25557 (70.34%)	15165 (74.78%)	9023 (67.34%)	1369 (51.58%)	
Smoke status					< 0.001
Current or previous	16556 (45.57%)	8300 (40.93%)	6669 (49.77%)	1587 (59.80%)	
Never	19776 (54.43%)	11979 (59.07%)	6730 (50.23%)	1067 (40.20%)	
Sleep duration, minutes	7.00 [7.00, 8.00]	7.00 [7.00, 8.00]	7.00 [6.00, 8.00]	7.00 [6.00, 8.00]	0.161
Sedentary time, hours	4.50 [3.00, 6.00]	4.00 [3.00, 6.00]	5.00 [3.50, 6.00]	5.00 [4.00, 7.00]	< 0.001
Physical activity, n (%)					< 0.001
Adequate	26075 (71.77%)	14225 (70.15%)	9755 (72.80%)	2095 (78.94%)	
Inadequate	10257 (28.23%)	6054 (29.85%)	3644 (27.20%)	559 (21.06%)	

BMI: body mass index; CRP: C-reactive protein; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; Categorical variables are presented as numbers (percentages), while continuous variables are expressed as median (interquartile range, IQR) or mean (standard deviation, SD).

Age, years	Total (36332)	Nonfrail (20279)	Prefrail (13399)	Frail (2654)	P value
	56.83 ± 8.16	**55.88 ± 8.24**	**57.87 ± 7.97**	**58.80 ± 7.53**	**< 0.001**
Diabetes mellitus, n (%)	2189 (6.02%)	431 (2.13%)	1218 (9.09%)	540 (20.35%)	< 0.001
History of hypertension, n (%)	20103 (55.33%)	9914 (48.89%)	8275 (61.76%)	1914 (72.12%)	< 0.001
History of hyperlipidemia, n (%)	6552 (18.03%)	1895 (9.34%)	3542 (26.43%)	1115 (42.01%)	< 0.001
Malignant tumor, n (%)	3046 (8.38%)	1146 (5.65%)	1485 (11.08%)	415 (15.64%)	< 0.001
Aspirin use, n (%)	5155 (14.19%)	1717 (8.47%)	2576 (19.23%)	862 (32.48%)	< 0.001
Insulin use, n (%)	406 (1.12%)	59 (0.29%)	232 (1.73%)	115 (4.33%)	< 0.001
Lipid-lowering use, n (%)	6601 (18.17%)	1742 (8.59%)	3626 (27.06%)	1233 (46.46%)	< 0.001

BMI: body mass index; CRP: C-reactive protein; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; Categorical variables are presented as numbers (percentages), while continuous variables are expressed as median (interquartile range, IQR) or mean (standard deviation, SD).

Plasma proteins associated with Frailty index

Based on multiple linear regression analyses, 956 proteins were significantly associated with FI among 2,911 proteins (FDR-adjusted P < 0.01, Fig. 2). Among these identified proteins, 838 showed positive correlations with FI, with the 5 most strongly associated proteins being Gastrin (GAST), Chromogranin-A (CHGA), V-set and immunoglobulin domain-containing protein 2 (VSIG2), Growth/differentiation factor 15 (GDF15), and WAP four-disulfide core domain protein 2 (WFDC2). In contrast, 118 proteins showed negative correlations with FI, with the top 5 most strongly associated proteins being A disintegrin and metalloproteinase with thrombospondin motifs 8 (ADAMTS8), Contactin-1(CNTN1), ITGA11 (Integrin alpha-11), LRRN1 (Leucine-rich repeat neuronal protein 1), and POMC (Pro-opiomelanocortin). The association between the levels of the proteins most strongly associated with FI and changes in FI is shown in **Supplementary Fig. 1**.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the 956 FI-associated proteins revealed a pronounced signature of immune dysregulation, with predominant involvement in leukocyte migration and chemotaxis. Pathway analyses further highlighted significant

enrichment in cytokine-cytokine receptor interaction and virus protein-cytokine interaction pathways (**Supplementary Fig. 2**).

Construction of an FI-Associated Poly Protein Score

To distill a more parsimonious and robust proteomic signature, we applied least absolute shrinkage and selection operator (LASSO) regression and 210 key proteins were finally selected. These proteins were considered key for FI and were subsequently used to construct the PPS. The coefficients for each proteins used to construct PPS are showed in **Supplementary Table 1**.

In the full cohort, we investigated the association between PPS and mortality risk. The results indicated that after adjusting for multiple confounding factors, PPS levels were significantly associated with examined 6 mortality outcomes (Fig. 3). Specifically, each 1-SD increase in PPS was associated with a 93% higher risk of all-cause mortality, a 147% higher risk of digestive mortality, a 133% higher risk of cardiovascular disease mortality, a 134% higher risk of respiratory mortality, a 61% higher risk of cancer-related mortality, and a 65% higher risk of neurodegenerative mortality. Notably, the PPS outperformed the clinical FI itself in predicting all mortality outcomes and in death risk stratification (**Supplementary Fig. 3–4**). Association between PPS and various mortality outcomes remained robust across different frailty statuses, which powerfully demonstrates its predictive efficacy independent of the FI (**Supplementary Fig. 5**). In addition, decision curve analysis (DCA) indicated that PPS outperformed FI in guiding clinical decision-making in preventing mortality (**Supplementary Fig. 6**).

We extended our analysis to 33 outcomes across 6 systems, and the results indicated that PPS was significantly correlated with 32 (96.97%) of the diseases examined. Per 1-SD increase in PPS, the top five outcomes with the highest risk were liver cancer (HR: 3.08; 95% CI: 2.25–4.22), fibrosis and cirrhosis of liver (HR: 2.73; 95% CI: 2.45–3.04), metabolic dysfunction-associated steatotic liver disease (MASLD; HR: 1.90; 95% CI: 1.73–2.10), chronic liver disease (HR: 1.79; 95% CI: 1.68–1.91), and peripheral artery disease (HR: 1.78; 95% CI: 1.62–1.94). This broad association spectrum underscores that the PPS captures a systemic biological state predisposing to multi-organ dysfunction, with particularly strong links to hepatic and vascular pathologies.

Further stratification by sex and age revealed that the risks of 28 (84.85%) diseases were significantly associated with PPS across all subgroups (**Supplementary Tables 2–3**). In sensitivity analyses, excluding participants who developed an outcome within the first year of follow-up or those with missing covariate data yielded similar patterns of association between diseases and PPS (**Supplementary Tables 4**). We further conducted restricted cubic spline (RCS) analyses on the 6 mortality outcomes and the 28 diseases that were significantly associated with PPS in both stratified and sensitivity analyses to detect potential dose-response relationships. The results indicated that PPS was generally linearly associated with adverse events (**Supplementary Fig. 7–11**).

Trajectory Analyses of FI-Associated Poly Protein Score

Given that proteins are products of gene-environment interactions and exhibit dynamic evolution, we conducted temporal trajectory analyses to explore the level trajectories of PPS before the onset of major clinical outcomes using the pseudo-longitudinal nested case–control design. The trajectory analysis revealed that within the 15 years preceding all-cause mortality, PPS levels in the deceased group were consistently significantly higher than those in the control group ($P < 0.001$ for each time point, Fig. 4A). A particularly important finding is that in the 5 years leading up to death, PPS levels entered a channel of accelerated increase. This dual pattern, featuring both a “prediction window” and an “acceleration window”, holds significant clinical implications: first, the long-term sustained elevation of PPS establishes it as a highly promising ultra-early biomarker for all-cause mortality (the prediction window); second, its sharp increase may indicate that an individual has entered a “terminal stage” of high-risk of death (the acceleration window). Our further trajectory analyses with digestive, CVD, respiratory and cancer mortality as outcomes reinforced this consistent pattern (Fig. 4B-E).

However, in the trajectory analysis with neurodegenerative mortality as the outcome, although the PPS levels of participants who experienced the outcome were significantly higher than those of the controls at most time points before the event, no accelerating upward trend in PPS was observed in the period immediately preceding the outcome (Fig. 4F). This is likely due to a data limitation: at the − 1 and − 2 year time points, no individuals were available for the trajectory analysis. This indicates that no participants in this study cohort died from neurodegenerative diseases within the first two years of follow-up, thus preventing us from capturing the trajectory of PPS before neurodegenerative death. Additionally, an interesting finding is that at the − 3 year time point, the mean PPS of the case group was even slightly lower than that of the control group, although this difference was not statistically significant. This may be a bias caused by the small sample size ($n = 3$) at this time point.

We further conducted temporal trajectory analyses for the 28 diseases that were significantly associated with PPS in both stratified and sensitive analyses (**Supplementary Fig. 12–15**). The results showed that within the 15 years preceding disease onset, PPS levels in the case group were significantly higher than those in the control group at the vast majority of time points. Furthermore, for several diseases, including peripheral artery disease, heart failure, myocardial infarction, major adverse cardiac events (MACE), ischemic heart disease, atrial fibrillation, and all-cause dementia, an accelerating upward trend in PPS was observed in the years immediately preceding the outcome. This suggests that a chronically elevated PPS can serve as an ultra-early warning signal for these diseases, while a longitudinal increase in an individual’s PPS is a strong indicator of imminent onset.

Pathway of FI-Associated Poly Protein Score and Mendelian randomization

The PPS we constructed has been demonstrated to be a powerful predictor of mortality and multisystem diseases. To gain a deeper understanding of its underlying biological basis, we performed functional annotation on the 210 constituent proteins of this score to decipher the core biology captured by the PPS. Notably, these proteins are not random inflammatory markers but are functionally concentrated in orchestrating pathogen-host interactions and modulating leukocyte proliferation (**Supplementary**

Fig. 16). Pathway analysis indicates that these proteins are significantly enriched in cytokine-cytokine receptor interaction, the PI3K-Akt signaling pathway, and extracellular matrix (ECM) receptor interaction. In particular, the significant enrichment of these proteins in virus-cell interaction pathways, provides a molecular correlation for the clinically observed susceptibility of frail individuals to infections. Thus, the PPS appears to quantify a state of altered immune homeostasis that underlies frail individuals' systemic vulnerability.

We employed two-sample MR analysis to investigate the potential causal relationship between FI and the proteins used to construct the PPS. After stringent multiple testing correction (FDR < 0.05), we identified 12 plasma proteins with causal associations with the FI (**Supplementary Tables 5**). Among them, genetically predicted higher levels of Myelin-oligodendrocyte glycoprotein (MOG; b = 0.659, FDR-adjusted P = 2.56E-12) and Fibroblast growth factor receptor 2 (FGFR2; b = 0.430, FDR-adjusted P = 9.17E-06) were the strongest risk factors for frailty; conversely, higher levels of Chymotrypsin-like elastase family member 2A (CELA2A; b = -0.099, FDR-adjusted P = 5.04E-11) and Cytokine receptor-like factor 1(CRLF1; b = -0.051, FDR-adjusted P = 9.01E-07) showed significant protective effects. The F statistics for all genetic instruments ranged from 20 to 753, with no weak instruments identified (**Supplementary Tables 6**). Steiger filtering was performed to confirm that all causal directions were from protein levels to frailty, thereby supporting the robustness of our findings.

For 5 proteins identified as promoting frailty through MR, we conducted drug prediction based on the DGIdb database (**Supplementary Tables 7**). Ultimately, we identified 98 potential drugs targeting FGFR2 and CD14, among which 30 drugs have already been approved and are applicable for antitumor, antidiabetic, antihyperlipidemic, and anti-inflammatory therapies. Additionally, we identified 68 previously unreported drugs, opening up new potential avenues for frailty intervention.

3. Discussion

The main findings of this study are as follows: (1) We identified 956 proteins significantly associated with the FI from 2,911 plasma proteins, with GAST and CHGA showing the strongest positive associations, and ADAMTS8 and CNTN1 showing the strongest negative associations. (2) Based on 210 key proteins selected by LASSO regression, we constructed a PPS and demonstrated its strong association with mortality risk and the incidence of multisystem diseases. (3) Trajectory analyses revealed that the PPS exhibits a dual-pattern model with a "prediction window" and an "acceleration window", indicating it serves as both an ultra-early risk factor for mortality and a warning signal for a sharp increase in short-term mortality risk. (4) We annotated the core biological processes captured by the PPS; furthermore, MR analysis identified 12 plasma proteins with a causal association with the FI, and 98 potential frailty intervention drugs targeting FGFR2 and CD14 were further screened based on drug-target interaction predictions.

This study identified 956 plasma proteins significantly associated with FI out of 2,911, mapping a broad molecular landscape for understanding the biological basis of frailty. Among them, GAST and CgA

showed the strongest positive correlations. As a gastrointestinal hormone, GAST has been demonstrated to act as an immune-modulating hormone, and its concentration is linked to the aging process[15, 16]. CgA is widely present in the secretory granules of neuroendocrine cells, where it can influence macrophage activity and cytokine release, serving as a critical bridge between the neuroendocrine and immune systems[17, 18]. Elevated plasma CgA levels have been demonstrated to be closely associated with cardiovascular diseases, tumors, and mortality risk[19, 20]. ADAMTS8 and CNTN1 exhibited the strongest negative associations with the FI. ADAMTS8 is a protein involved in ECM remodeling and participates in anti-angiogenic processes, playing a crucial role in maintaining ECM homeostasis. Reduced levels of ADAMTS8 may lead to an imbalance in ECM remodeling, subsequently promoting aging-related phenotypes such as tissue fibrosis, vascular stiffening, and endothelial dysfunction[21, 22]. CNTN1 is primarily expressed in the central nervous system and serves as a frailty-related protective protein[23, 24]. Its plasma levels have been demonstrated to be associated with core phenotypic manifestations of frailty, such as impaired mobility and reduced muscle strength[25].

In summary, the proteins most closely associated with the FI are predominantly enriched in biological processes such as chronic inflammation/immunity and tissue repair. This conclusion is further supported by GO and KEGG functional enrichment analyses: in the GO analysis, the highest-ranking functional terms are “leukocyte migration” and “leukocyte chemotaxis”; in the KEGG pathway analysis, the most significantly enriched pathway is “cytokine-cytokine receptor interaction”—regarded as the “core signaling axis” of inflammatory regulation. Together, these results indicate that the bodies of frail individuals are in a state of sustained, low-grade systemic inflammation. Additionally, the significant enrichment of the “ECM-receptor interaction” pathway in the KEGG analysis suggests that dysregulation of extracellular matrix homeostasis and impaired tissue repair function play an important role in the development and progression of frailty.

The frailty-related PPS constructed based on 210 key proteins selected by LASSO regression, demonstrates strong clinical predictive and application potential for mortality and multi-system diseases. This study found that the efficacy of PPS in predicting all-cause and cause-specific mortality significantly outperformed the clinical FI itself. Also, the strong association between PPS and mortality risk remained consistent across subgroups with different frailty statuses. This indicates that PPS captures a deeper biological risk independent of clinical manifestations. Even in individuals who do not yet exhibit obvious frailty symptoms, an elevated PPS already signals a higher risk of mortality, providing an objective molecular basis for distinguishing “preclinical frailty” and “biological frailty”.

FI can be changed following effective interventions, which include strategies such as supplementation targeting specific proteins[4, 26]. Therefore, it is crucial to evaluate the dynamic trajectory of the FI-PPS and its relationship with mortality and disease risk. Based on temporal trajectory analyses, we reveals a unique evolutionary pattern of PPS in predicting mortality risk—a dual-pattern model characterized by coexisting “prediction window” and “acceleration window”.

Our findings highlight two key insights: First, PPS shows a sustained elevation as early as 15 years before a mortality event, indicating its potential as an ultra-early screening tool to identify individuals at elevated future mortality risk, thereby providing a valuable time window for implementing long-term preventive interventions. Second, the sharp upward trend of PPS observed during the “acceleration window” within five years prior to death may signal that an individual has entered a “decompensation turning point” or “terminal stage” of physiological reserve. The rapid increase in PPS during this phase serves as a strong warning signal of rapid disease deterioration and a sharp rise in mortality risk. Therefore, for individuals with persistently elevated PPS levels, especially those with a recent rapid increase, a comprehensive and proactive medical evaluation should be initiated immediately.

In this study, we performed enrichment analyses on two distinct protein sets: 956 proteins associated with the FI and 211 core proteins used to construct the PPS. The analysis of the FI-associated proteins aimed to systematically delineate the overall molecular landscape of frailty, while the analysis of the PPS core proteins sought to reveal the underlying biological mechanisms of PPS as a predictive tool. GO enrichment analysis revealed that the proteins constituting the PPS are significantly enriched in biological processes integral to pathogen-host interactions and the regulation of immune cell proliferation. Notably, terms such as “viral entry into host cell”, “entry into host cell”, and “movement in host” were highly enriched. Furthermore, KEGG pathway analysis identified significant enrichment in “cytokine-cytokine receptor interaction” and “viral protein interaction with cytokine and cytokine receptor” pathways. Together, these findings link the biological state quantified by the PPS to the host’s defense response against pathogen invasion. This is consistent with previous research indicating that pathogen infection is a key factor in the development of frailty[27, 28]. This sustained immune activation driven by persistent or recurrent infectious, may represent a key upstream event that drives chronic systemic inflammation and ultimately depletes physiological reserves. This process also constitutes the core predictive mechanism captured by the PPS as a predictive tool.

We conducted MR to infer potential causal relationships between specific plasma proteins and frailty, identifying 5 risk proteins and 7 protective proteins associated with frailty. Based on these findings, we conducted drug-target interaction predictions for the identified risk proteins, successfully screening 98 potential frailty intervention drugs targeting FGFR2 and CD14. Among these, 30 drugs are already approved, providing a candidate drug list for the “drug repurposing” strategy in frailty. FGFR2 inhibitors have already been used in the treatment of various tumors and fibrotic diseases, and our results suggest that FGFR2 inhibitors may represent a feasible strategy for intervening in frailty[29, 30]. In addition, the drugs predicted for CD14 provide evidence for testing the hypothesis that inhibiting excessive activation of innate immunity can improve frailty.

This study systematically delineated the plasma proteomic profile of frailty, constructed a predictive PPS for death and multi-morbidity, and explored potential intervention drugs for frailty. However, our research still has certain limitations.

First, there are inherent limitations in the study design. Although MR were employed, the association analysis between proteins and the FI is inherently cross-sectional, making it difficult to completely rule out the possibilities of reverse causality or residual confounding biases. Furthermore, proteomic measurements were obtained at baseline only; thus, our trajectory analyses represent population-level patterns across different times to event rather than within-individual changes. Although the observed “acceleration window” in the trajectory analysis is suggestive, it requires validation in study designs that incorporate more intensive, prospective biomarker monitoring.

Second, caution is warranted when extrapolating the findings to other populations. UK Biobank participants are predominantly of European ancestry and exhibit a “healthy volunteer” bias, as the cohort is relatively healthier and of higher socioeconomic status.

Third, the construction of the FI relies on self-reported deficits, which may introduce measurement errors and biases.

Additionally, the established mechanisms and the translation of drug predictions require further validation. The causal associations suggested by MR need subsequent validation in cell and animal experiments. Moreover, the drug predictions are based on computational databases, and the translational potential of the identified drugs ultimately requires confirmation through clinical trials.

Finally, some results are constrained by statistical power. For example, in the trajectory analysis of neurodegenerative disease mortality, the lack of early death cases prevented the capture of the complete pattern of the “acceleration window”. The limited sample size in certain subgroup analyses, specifically for rare diseases, may affect the precision and stability of the estimated associations.

In summary, we identified proteins associated with FI and constructed a frailty-related PPS that demonstrates predictive value for mortality and multiple diseases. This score exhibits a dual-pattern model in predicting the risks of mortality and various diseases, combining long-term predictive capability with short-term warning functions. Furthermore, we identified FI-risk proteins and successfully screened candidate drugs with potential therapeutic value.

4. Methods

Ethics statement

The UK Biobank study received ethics approval from the North West Multi-Center Research Ethics Committee (MREC, reference number: 21/NW/0157), and all participant have provided written informed consent[31]. Our study was conducted under UK Biobank project number 100739.

Study population

This study was conducted based on the prospective cohort of UK Biobank. From 2006 to 2010, the UK Biobank recruited over 500,000 participants across 22 assessment centers. Participants were included if

they had proteomic data at baseline. The exclusion criteria were: (1) more than 10 missing items of FI, and (2) missing proteomic data exceeding 20%.

Definition of frailty index

FI was constructed from 49 self-reported items, which covered disease, physical activity, and mental health[32]. For individuals with fewer than 10 missing items, the FI was calculated as the ratio of the number of present deficits to the total number of possible deficits, yielding a value ranging from 0 to 1[3]. Participants are classified as frail (> 0.24), prefrail (0.12–0.24), or nonfrail (< 0.12). Details of FI Calculation were showed in **Supplementary Table 8**.

Assessment of mortality and multi-morbidity

Primary outcome of this study was all-cause mortality. To investigate the risk of cause-specific death, we also analyzed the following mortality-related outcomes: digestive, cardiovascular, respiratory, cancer, and neurodegenerative mortality. The analysis of mortality-related outcomes was performed in the full cohort. To explore the association between the PPS we constructed and diseases of different systems, we defined 33 diseases across six systems. These systems included: “cardiovascular disorders”, “neurological and mental diseases”, “digestive system disorders”, “musculoskeletal system disorders”, “respiratory system disorders”, and “endocrine and metabolism disorders”. To analyze 33 diseases and ensure statistical power (given the low positive event rate for some conditions, such as 0.10% for liver cancer), we constructed separate cohorts for each disease, excluding participants who had the disease at baseline. The censoring date was defined as the earliest of the date of first event, death, or the last follow-up date. Assessment of mortality and multi-morbidity were showed in **Supplementary Table 9**.

Covariates

We controlled for a range of potential confounders, including demographic factors (age, sex, waist circumference, body mass index, ethnicity), socioeconomic indicators (education, household income, unemployment, Townsend deprivation index), biochemical markers (C-reactive protein, glycated hemoglobin, eGFR), lifestyle behaviors (smoking, alcohol, sleep, sedentary time, physical activity), and medical history (hypertension, hyperlipidemia, diabetes mellitus, cancer; use of aspirin, insulin, lipid-lowering drugs). Sufficient physical activity was considered as achieving a minimum of 150 minutes per week, calculated as vigorous activity minutes plus twice the moderate activity minutes.

Proteomics data

This study utilized plasma proteomic data from the UK Biobank Pharma Proteomics Project (UKB-PPP). Sample collection, protein quantification, and quality control procedures followed established protocols[33]. In brief, baseline plasma samples from 53,016 participants were analyzed using the Olink platform, and 2,920 proteins were quantified. Proteins with > 20% missing values were excluded, and

2,911 proteins were finally included for analysis. All protein levels were standardized prior to statistical evaluation.

Statistical analysis

(1) Data description and imputation:

Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Accordingly, continuous variables were presented as mean±standard deviation (SD) or median with interquartile range (IQR), while categorical variables are expressed as frequency with percentage. Chi-square test was conducted for categorical variables for intergroup comparisons, analysis of variance (ANOVA) was conducted for normally distributed continuous variables, and the Kruskal-Wallis test was conducted for non-normally distributed continuous variables. For proteins and covariates with missing data, we conducted data imputation by multiple imputation chained equations (MICE).

(2) Identification of FI-associated plasma proteins:

Multiple linear regression analyses were employed to examine the cross-sectional associations between each plasma protein level and the FI, with comprehensive adjustment for all covariates. The false discovery rate (FDR) method was applied to correct for multiple testing across all proteins, and proteins with an FDR-adjusted p-value < 0.01 were considered significantly associated with FI. GO and KEGG pathway enrichment analyses were performed on the significantly associated proteins to elucidate the involved biological processes and signaling pathways.

(3) Construction and validation the PPS:

To identify a robust and parsimonious set of core proteins from the candidate proteins, we utilized a stability selection framework incorporating LASSO regression. This approach minimizes the inclusion of spurious variables and enhances the reliability of the feature selection. The procedure involved 1,000 iterations, each fitting a LASSO model to a random 80% subsample of the population. Frailty status served as the outcome, with candidate proteins as predictors. The optimal regularization parameter (λ) was determined using 10-fold cross-validation, and the lambda.1se value was selected to favor a more parsimonious model. The selection frequency for each protein—defined as the proportion of iterations where its coefficient was non-zero—was then calculated. Proteins selected in at least 90% of iterations were retained as the final robust protein set for downstream analysis. Based on the core proteins selected through the stability selection process, we constructed the frailty-associated PPS. First, in the complete dataset, the levels of the ultimately selected proteins were standardized using Z-score normalization. Subsequently, the standardized weight for each protein was obtained by fitting a final LASSO regression model. Finally, the PPS for each participant was calculated as a weighted linear combination of the standardized protein levels and their corresponding regression coefficients according to the formula:

$$PPS = \sum_{i=1}^{J} \beta_i \times (Protein_i level)$$

PPS serves as an integrated metric for quantifying an individual's systemic frailty risk and is utilized for subsequent association analyses and trajectory assessment.

The association between the PPS and the risks of various mortality outcome and incident diseases was evaluated using Cox proportional hazards models, adjusted for all covariates. HR and related 95% CI were reported. The predictive performance of the PPS was compared to that of the clinical FI using the Receiver Operating Characteristic (ROC) curve. Sensitive analyses were conducted by excluding participants who developed the outcome within the first year of follow-up or had missing covariate data. Stratified analyses by sex and age groups were also performed. Restricted cubic splines were used to examine the potential nonlinear dose-response relationship between PPS and the outcomes.

(4) Study design for pre-diagnostic trajectory analyses

We conducted a nested case–control study with incidence density sampling to characterize population-level pre-event patterns of baseline PPS prior to clinical outcome[34]. This approach minimizes survivor bias and incorporates the time-varying risk sets of the cohort. For each incident case identified during follow-up, we matched up to 10 controls from the corresponding risk set. The risk set was defined as participants who were alive, under follow-up, and outcome-free. Matching was based on baseline age (± 2 years) and duration of follow-up to ensure the comparability of risk windows between cases and controls. This sampling strategy enables a valid comparison of biomarker profiles between cases and controls at identical time intervals preceding the clinical manifestation of the disease.

To construct the temporal trajectory of the PPS, we retrospectively aligned baseline plasma samples according to the time-to-event scale. The study period was divided into one-year intervals, mapping each participant’s baseline biomarker levels to a specific remaining time before the index diagnosis. This approach successfully transforms the cross-sectional baseline data into pseudo-longitudinal trajectories, spanning from 15 years prior to diagnosis up to the time of the event. Notably, proteomic measurements were obtained at baseline only, thus these trajectories reflect population-level differences across varying times to event rather than within-individual longitudinal changes. At each time point, we used Student’s t-tests to compare the mean standardized PPS levels between cases and matched controls. The goals of this trajectory analysis were as followed:

Identify the divergence time: The earliest point where PPS levels in future cases significantly diverged from controls, which defines the potential window for early detection.

Characterize the changing trajectory: To visualize and examine the dynamic evolutionary trend of the PPS from 15 years before diagnosis until the event occurred.

(5) Mendelian randomization and Drug prediction

To explore whether frailty-related plasma proteins may play a causal role in frailty, we conducted two-sample MR. Cis-acting genetic variants associated with circulating protein concentrations at genome-wide significance ($P < 5\times10^{-8}$) were obtained from a large proteome-wide pQTL study involving 35,559 participants and used as instrumental variables for each protein. Summary statistics for the FI were derived from a genome-wide association meta-analysis including 175,226 individuals of European ancestry. Instrumental variants were aligned between datasets and pruned for linkage disequilibrium using a European ancestry reference panel to ensure independence of instruments. Causal effects were estimated primarily using inverse-variance weighted MR within a random-effects framework, with complementary sensitivity approaches applied to assess robustness to potential horizontal pleiotropy. Instrument strength and causal direction were evaluated to reduce bias from weak instruments and reverse causation, and multiple testing was controlled using the false discovery rate. Only protein–frailty associations consistently passing these validity checks were interpreted as having evidence for causality. Full analytical specifications, including instrument selection criteria, linkage disequilibrium thresholds, sensitivity procedures, and software implementation, are provided in the **Supplementary Methods 1**. In addition, to further explore potential drugs for managing frailty, we utilized the DGIdb (https://www.dgidb.org/) to predict drugs that may reduce the FI[35].

Declarations

Contributors

K H conceived, designed, and supervised this study. JT X implemented statistical analysis and manuscript draft. ZS H conducted data collection and PRS calculation. YF S checked the manuscript, and accessed and verified the underlying data reported in the manuscript. LL Land RN S modified the format of this article. CY X and JH H modified the grammar of this article. All authors had full access to all the data in the study and accept the responsibility to submit it for publication.

Data sharing statement

Data supporting the findings of this study are available at https://ams.ukbiobank.ac.uk/. As these data were used under the current research license, they are not publicly available. However, upon reasonable request and with the permission of the UK Biobank, data can be obtained from Kai Huang (huangk37@mail.sysu.edu.cn).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical abstract

FI: Frailty index; PPS: poly protein score; LASSO: least absolute shrinkage and selection operator; CD302: C-type lectin domain family 2 member D; FGFR2: Fibroblast growth factor receptor 2

Funding

The study is sponsored by Clinical High-tech, Major and Featured Technology Construction Project of Guangzhou (2026P-ZD017).

Acknowledgements

None.

Data Availability

Data supporting the findings of this study are available at https://ams.ukbiobank.ac.uk/. As these data were used under the current research license, they are not publicly available. However, upon reasonable request and with the permission of the UK Biobank, data can be obtained from Kai Huang (huangk37@mail.sysu.edu.cn).

References

1. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.
2. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376–86.
3. Zhong Q, Zhou R, Huang YN, Huang RD, Li FR, Chen HW, et al. Frailty and risk of metabolic dysfunction-associated steatotic liver disease and other chronic liver diseases. J Hepatol. 2025;82(3):427–37.
4. He D, Wang Z, Li J, Yu K, He Y, He X, et al. Changes in frailty and incident cardiovascular disease in three prospective cohorts. Eur Heart J. 2024;45(12):1058–68.
5. Ward DD, Flint JP, Littlejohns TJ, Foote IF, Canevelli M, Wallace LMK, et al. Frailty Trajectories Preceding Dementia in the US and UK. JAMA Neurol. 2025;82(1):61–71.
6. Foote IF, Flint JP, Fürtjes AE, Lawrence JM, Mullin DS, Fisk JD, et al. Uncovering the multivariate genetic architecture of frailty with genomic structural equation modeling. Nat Genet. 2025;57(8):1848–59.
7. Mak JKL, Qin C, Krüger M, Kuukka A, Hägg S, Lin J, et al. Large-scale genome-wide analyses with proteomics integration reveal novel loci and biological insights into frailty. Nat Aging. 2025;5(8):1589–600.

8. Livshits G, Ni Lochlainn M, Malkin I, Bowyer R, Verdi S, Steves CJ, et al. Shared genetic influence on frailty and chronic widespread pain: a study from TwinsUK. Age Ageing. 2018;47(1):119–25.
9. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505–22.
10. Mishra M, Wu J, Kane AE, Howlett SE. The intersection of frailty and metabolism. Cell Metab. 2024;36(5):893–911.
11. Ma LZ, Liu WS, He Y, Zhang Y, You J, Feng JF, et al. Plasma proteomics identify novel biomarkers and dynamic patterns of biological aging. J Adv Res. 2025.
12. Bourgault J, Abner E, Manikpurage HD, Pujol-Gualdo N, Laisk T, Gobeil É, et al. Proteome-Wide Mendelian Randomization Identifies Causal Links Between Blood Proteins and Acute Pancreatitis. Gastroenterology. 2023;164(6):953 – 65.e3.
13. Xu J, Liu J, Tang J, Liao J, Liu X, Odden MC, et al. Plasma proteomic signature of risk and prognosis of frailty in the UK Biobank. Geroscience. 2025;47(2):2365–81.
14. Rao Z, Wang S, Li A, Blaha MJ, Coresh J, Ganz P, et al. A Novel Longitudinal Proteomic Aging Index Predicts Mortality, Multimorbidity, and Frailty in Older Adults. Aging Cell. 2026;25(1):e70317.
15. Goldschmiedt M, Barnett CC, Schwarz BE, Karnes WE, Redfern JS, Feldman M. Effect of age on gastric acid secretion and serum gastrin concentrations in healthy men and women. Gastroenterology. 1991;101(4):977–90.
16. van Niekerk G, Kelchtermans L, Broeckhoven E, Coelmont L, Alpizar YA, Dallmeier K. Cholecystokinin and gastrin as immune modulating hormones: Implications and applications. Cytokine Growth Factor Rev. 2024;80:37–46.
17. Muntjewerff EM, Christoffersson G, Mahata SK, van den Bogaart G. Putative regulation of macrophage-mediated inflammation by catestatin. Trends Immunol. 2022;43(1):41–50.
18. Maj M, Hernik K, Tyszkiewicz K, Owe-Larsson M, Sztokfisz-Ignasiak A, Malejczyk J, et al. A complex role of chromogranin A and its peptides in inflammation, autoimmunity, and infections. Front Immunol. 2025;16:1567874.
19. Mahata SK, Corti A. Chromogranin A and its fragments in cardiovascular, immunometabolic, and cancer regulation. Ann N Y Acad Sci. 2019;1455(1):34–58.
20. Meng QH, Halfdanarson TR, Bornhorst JA, Jann H, Shaheen S, Shi RZ, et al. Circulating Chromogranin A as a Surveillance Biomarker in Patients with Carcinoids-The CASPAR Study. Clin Cancer Res. 2024;30(24):5559–67.
21. Badshah, II, Brown S, Weibel L, Rose A, Way B, Sebire N, et al. Differential expression of secreted factors SOSTDC1 and ADAMTS8 cause profibrotic changes in linear morphoea fibroblasts. Br J Dermatol. 2019;180(5):1135–49.
22. Omura J, Satoh K, Kikuchi N, Satoh T, Kurosawa R, Nogi M, et al. ADAMTS8 Promotes the Development of Pulmonary Arterial Hypertension and Right Ventricular Failure: A Possible Novel Therapeutic Target. Circ Res. 2019;125(10):884–906.

23. Liu F, Schrack JA, Walston J, Mathias RA, Windham BG, Grams ME, et al. Mid-life plasma proteins associated with late-life prefrailty and frailty: a proteomic analysis. Geroscience. 2024;46(5):5247–65.
24. Liu F, Schrack JA, Walker KA, Walston J, Mathias RA, Griswold ME, et al. The effect of long-term adherence to physical activity recommendations in midlife on plasma proteins associated with frailty in the Atherosclerosis Risk in Communities (ARIC) study. Eur J Epidemiol. 2025.
25. Osawa Y, Semba RD, Fantoni G, Candia J, Biancotto A, Tanaka T, et al. Plasma proteomic signature of the risk of developing mobility disability: A 9-year follow-up. Aging Cell. 2020;19(4):e13132.
26. Travers J, Romero-Ortuno R, Bailey J, Cooney MT. Delaying and reversing frailty: a systematic review of primary care interventions. Br J Gen Pract. 2019;69(678):e61-e9.
27. Strain JF, Cooley S, Kilgore C, Nelson B, Doyle J, Thompson R, et al. The Structural and Functional Correlates of Frailty in Persons With Human Immunodeficiency Virus. Clin Infect Dis. 2022;75(10):1740–6.
28. Vetrano DL, Triolo F, Maggi S, Malley R, Jackson TA, Poscia A, et al. Fostering healthy aging: The interdependency of infections, immunity and frailty. Ageing Res Rev. 2021;69:101351.
29. Zingg D, Bhin J, Yemelyanenko J, Kas SM, Rolfs F, Lutz C, et al. Truncated FGFR2 is a clinically actionable oncogene in multiple cancers. Nature. 2022;608(7923):609–17.
30. Auyeung VC, Steinberg TL, Olivier A, Suzuki L, Moreno ME, Khan IS, et al. Pharmacologic inhibition of IRE1α-dependent decay protects alveolar epithelial identity and prevents pulmonary fibrosis in mice. J Clin Invest. 2025;135(20).
31. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
32. Williams DM, Jylhävä J, Pedersen NL, Hägg S. A Frailty Index for UK Biobank Participants. J Gerontol A Biol Sci Med Sci. 2019;74(4):582–7.
33. Sun BB, Chiou J, Traylor M, Benner C, Hsu YH, Richardson TG, et al. Plasma proteomic associations with genetics and health in the UK Biobank. Nature. 2023;622(7982):329–38.
34. Beaumont JJ, Steenland K, Minton A, Meyer S. A computer program for incidence density sampling of controls in case-control studies nested within occupational cohort studies. Am J Epidemiol. 1989;129(1):212–9.
35. Cannon M, Stevenson J, Stahl K, Basu R, Coffman A, Kiwala S, et al. DGIdb 5.0: rebuilding the drug-gene interaction database for precision medicine and drug discovery platforms. Nucleic Acids Res. 2024;52(D1):D1227-d35.

Graphical Abstract

The graphical abstract is not available with this version.

Graphical abstract

FI: Frailty index; PPS: poly protein score; LASSO: least absolute shrinkage and selection operator; CD302: C-type lectin domain family 2 member D; FGFR2: Fibroblast growth factor receptor 2

Figures

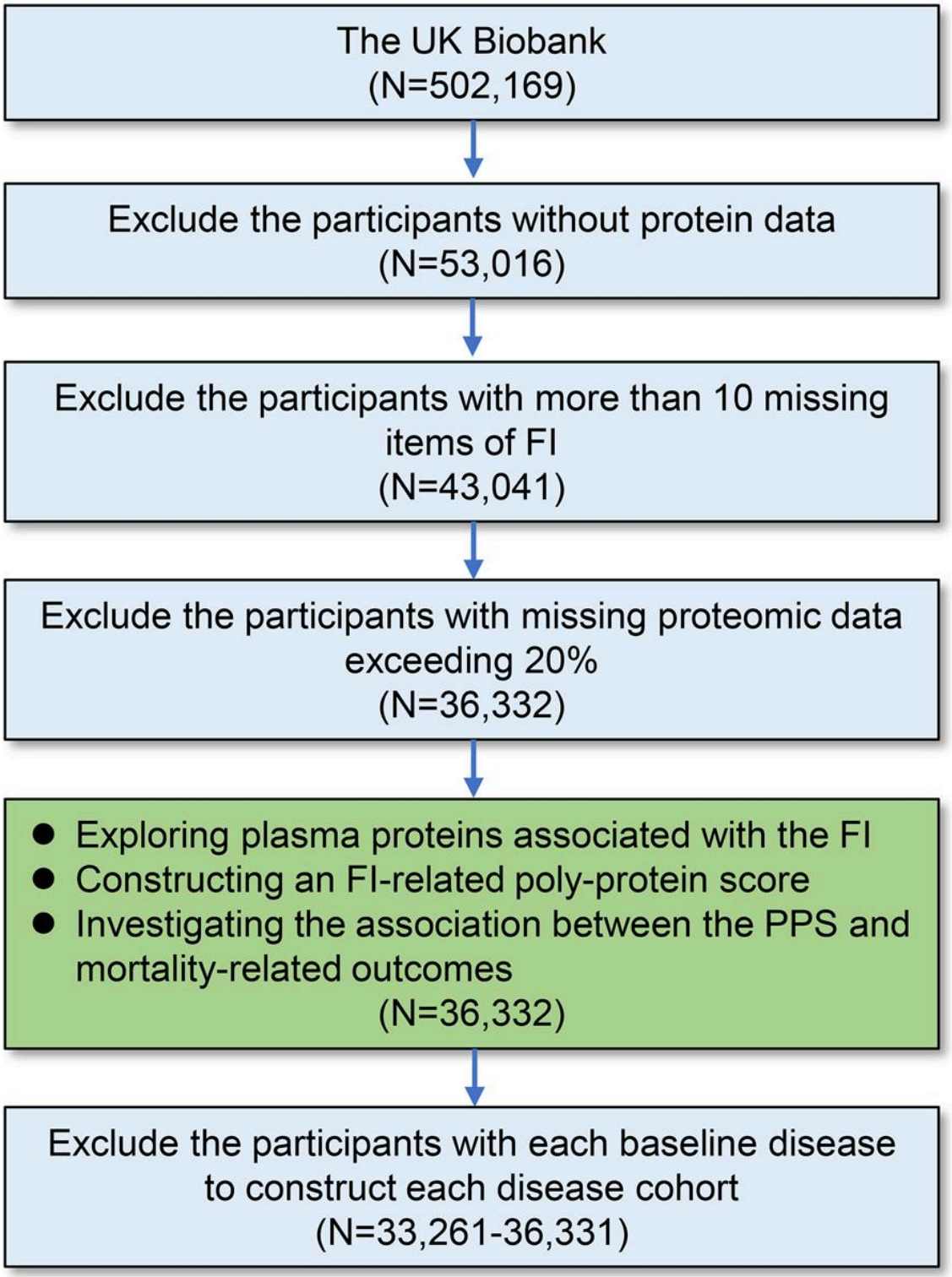


Figure 1

Flowchart for the selection of the analyzed cohorts in this study.

FI: Frailty index; PPS: poly protein score;

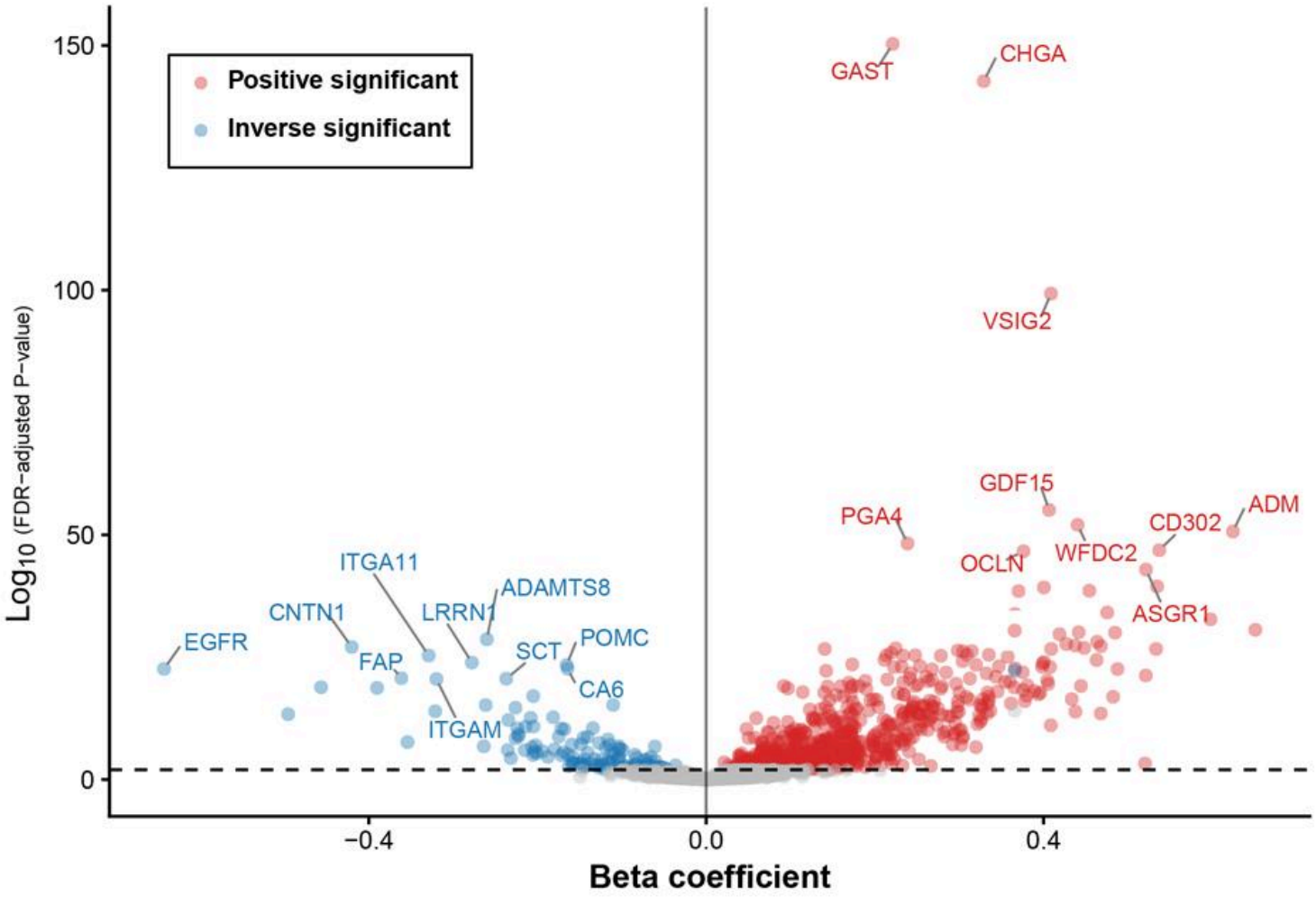


Figure 2

Associations between plasma proteins and FI level.

FDR: false discovery rate; HR: hazard ratios; GAST: gastrin; CHGA: chromogranin A; VSIG2: V-set and immunoglobulin domain containing 2; PGA4: pepsinogen 4; GDF15: growth differentiation factor 15; WFDC2: WAP four-disulfide core domain protein 2; CD302: C-type lectin domain family 2 member D; ASGR1: asialoglycoprotein receptor 1; ADM: adrenomedullin; OCLN; Occludin; ITGA11: Integrin Alpha 11; ADAMTS8: ADAM Metallopeptidase With Thrombospondin Type 1 Motif 8; CNTN1: Contactin 1; LRRN1: Leucine Rich Repeat Neuronal 1; SCT: Secretin; POMC: Proopiomelanocortin; EGFR: Epidermal Growth Factor Receptor; FAP: Fibroblast Activation Protein Alpha; ITGAM: Integrin Subunit Alpha M; CA6: Carbonic Anhydrase 6.

Multiple linear regression analyses with adjustment for age, sex, ethnicity, education level, body mass index, Townsend deprivation index, smoking status, alcohol intake frequency, sleep duration, waist

circumference, C-reactive protein, sedentary time, estimated glomerular filtration rate, glycated hemoglobin, household income, physical activity time, unemployment status, diabetes history, aspirin use, lipid-lowering drug use, cancer history, and hypercholesterolemia. A total of 956 proteins with an FDR-adjusted P-value < 0.01 were considered significantly associated with FI.

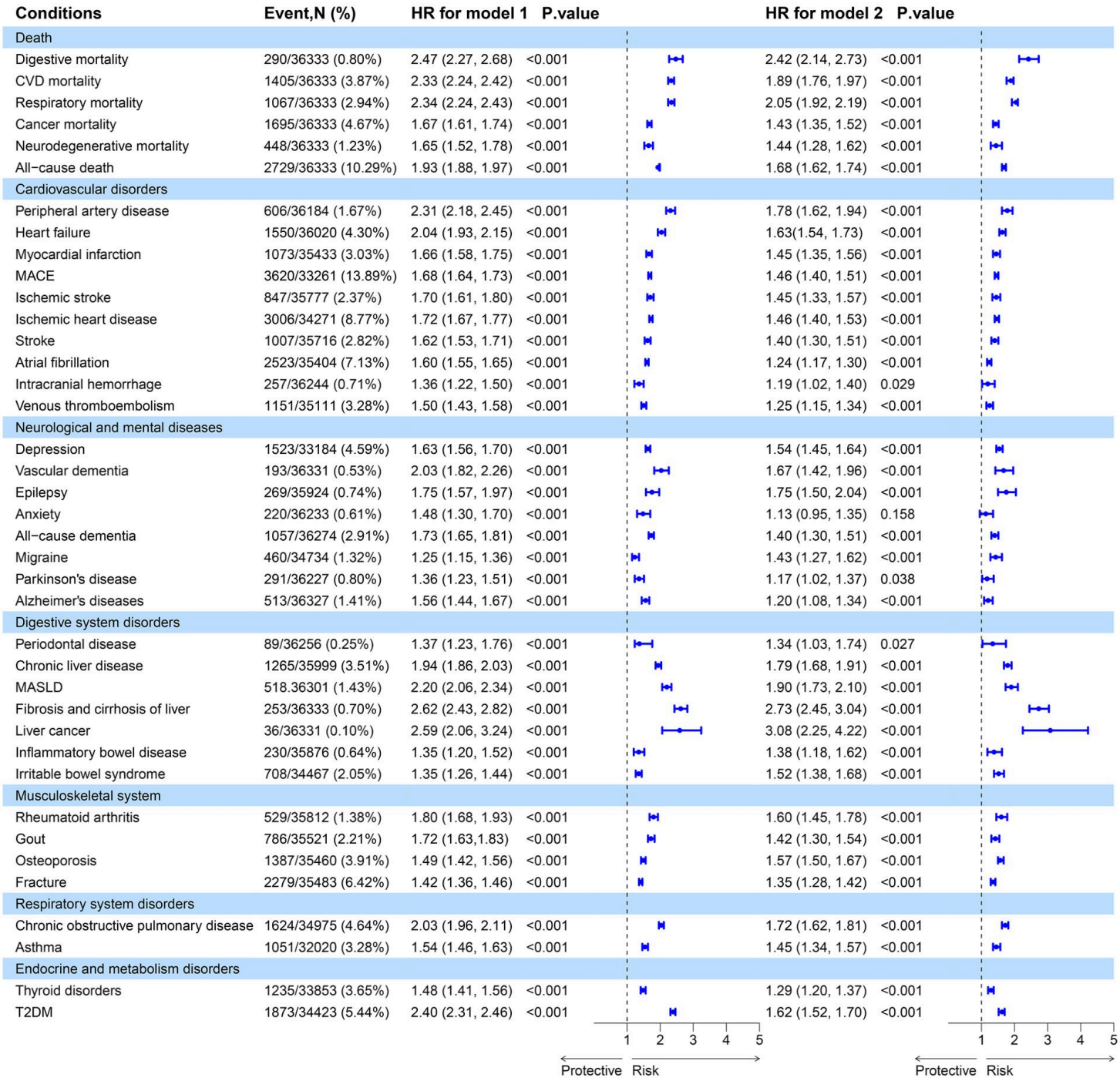


Figure 3

Association of weakness-related PPS with mortality and multi-morbidity.

FI: Frailty index; PPS: Frailty-associated Polyprotein Score; HR: Hazard ratio; SD: Standard deviation; CVD: Cardiovascular disease; MACE: major adverse cardiac events; MASLD: Metabolic dysfunction-associated

steatotic liver disease; T2DM: type 2 diabetes.

Models were based on multiple Cox regressions. The forest plot showed the magnitude of increases in risk of mortality and multi-morbidity for a 1-SD increase in the FI-PPS. Model 1 was adjusted for age, sex, ethnicity, education level, body mass index, deprivation index, smoking status, alcohol intake frequency, sleep duration, waist circumference, C-reactive protein, sedentary time, estimated glomerular filtration rate, glycated hemoglobin, household income, physical activity time, unemployment status, while Model 2 was adjusted for covariates in Model 1 plus diabetes history, aspirin use, lipid-lowering drug use, cancer history, and hypercholesterolemia.

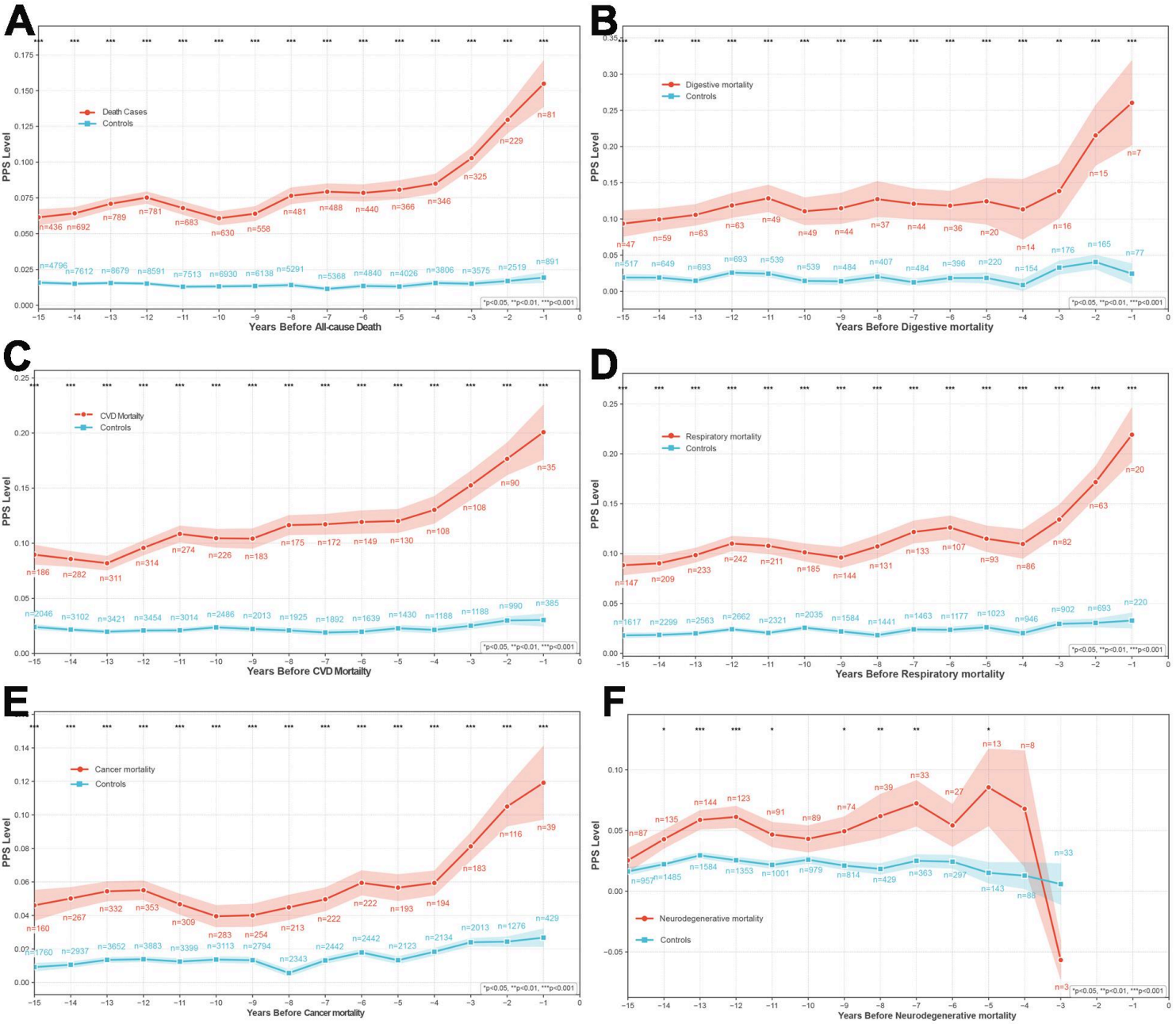


Figure 4

Temporal trajectory analyses to explore the level trajectories of PPS before the onset of mortality.

(A) Level trajectories of PPS before the onset of all-cause death.

(B) Level trajectories of PPS before the onset of digestive mortality.

(C) Level trajectories of PPS before the onset of CVD mortality.

(D) Level trajectories of PPS before the onset of respiratory mortality.

(E) Level trajectories of PPS before the onset of cancer mortality.

(F) Level trajectories of PPS before the onset of neurodegenerative mortality.

PPS: Frailty-associated Polyprotein Score; CVD: Cardiovascular disease.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure.docx
- SupplementaryTable.xlsx
- Supplementarymethod.docx